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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
16626 KB		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/HU 03/00096	13.11.2003	13.11.2002
International Patent Classification (IPC) or both national classification and IPC		
A61K31/501		
Applicant		
EGIS GYOGYSZERGYAR RT.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 1 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
09.06.2004	21.12.2004
Name and mailing address of the international preliminary examining authority:	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Friederich, M Telephone No. +49 89 2399-7860

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/HU 03/00096

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-34 as originally filed

Claims, Numbers

1-31 as originally filed

Drawings, Sheets

1/1 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 31 with respect to industrial applicability

   because:

   ☒ the said international application, or the said claims Nos. 31 relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-29,31
	No:	Claims	30
Inventive step (IS)	Yes:	Claims	1-29,31
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-30
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claim 31 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: WO 03/027078 A (EGYT GYOGYSZERVEGYESZETI GYAR ;KOMPAGNE HAJNALKA (HU); MIKLOSNE KO) 3 April 2003 (2003-04-03)
D2: WO 03/027097 A (EGYT GYOGYSZERVEGYESZETI GYAR ;KOMPAGNE HAJNALKA (HU); MIKLOSNE KO) 3 April 2003 (2003-04-03)
D3: EP-A-0 372 305 (CL PHARMA) 13 June 1990 (1990-06-13)

If not indicated otherwise, the relevant passages are those mentioned in the International search report.

Assuming a valid priority of the present application, the P-documents (D1 and D2) cited in the International search report are not dealt with during the PCT-procedure.

Art. 6 The terms "lower alkyl", "lower alkoxy" used in **claim 1** are vague and unclear and leave the reader in doubt as to the meaning of the technical features to which they refer, thereby rendering the definition of the subject-matter of said claim unclear.

Art. 33(2) The present application does not meet the requirements of Article 33(2)

PCT, because the subject-matter of **claim 30** does not appear to be new in the sense of Article 33(2) PCT. In interpreting claims for determining novelty, non distinctive characteristics of a particular intended use (see for example claim 30 "for the treatment of malfunctions of memory...") are disregarded. Hence, the subject matter of **claim 30** discloses nothing more than the composition per se.

D3 discloses the use of pyridazinone derivatives for the treatment of cardiovascular diseases and hypertension.

The subject-matter of the product **claim 30** is therefore not considered to be new (Article 33(2) PCT).

The subject-matter of **claims 1-29 and 31** is considered to be new in the sense of Article 33(2) PCT since the additional features delimit these claims from the prior art at hand.

Art. 33(3) The subject-matter of **claims 1-29 and 31** appears to meet the requirements of Article 33(3) PCT.

D3 discloses the use of pyridazinone derivatives for the treatment of cardiovascular diseases and hypertension.

The problem to be solved by the present invention may therefore be regarded as how to provide compounds for the treatment of neurodegenerative diseases.

The present application suggests to solve the problem posed by the use of the pyridazinone derivatives.

There is no hint in the prior art that these compounds can be used for the treatment of neurodegenerative diseases as this is shown for the compound of example 3 of the present application.

Therefore the subject-matter of **claims 1-29 and 31** is considered to involve an inventive step in the sense of Art. 33(3) PCT.

Art. 33(4) The subject-matter of **claims 1-30** is considered to be industrially applicable in the sense of Art. 33(4) PCT.

For the assessment of the present **claim 31** on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Table

Effect of the test compounds and the carrier, respectively, on the blood pressure and heart frequency of alert rats

Compound	Average blood pressure (Hgmm) Average	S.E.	Average	SE.	Δ (Hgmm)	Statistical evaluation
A	91.5	2.9	95.4	2.2	+3.9	N.S.
B	96.0	2.7	97.0	2.1	+1.0	N.S.
C	101.5	3.8	106.3	2.7	+4.8	N.S.
D	91.5	2.9	89.9	2.5	-1.6	N.S.
E	92.6	3.3	92.7	3.2	+0.1	N.S.
F	91.5	2.9	101.5	3.9	+10.0	N.S.
G	99.1	1.9	105.2	1.6	+6.1	N.S.

N.S. = not significant
S.E. = fault of the average

It can be seen from the above data that none of the test compounds exhibits antihypertensive effect.

A = 2-t-butyl-5-chloro-4-(2-(4-(2,3-dihydro-benzo[1,4]dioxine-5-yl)-piperazine-1-yl)-ethylamino)-2H-pyridazine-3-one

B = 4-chloro-5-((2-(4-(2,3-dihydro-benzo[1,4]dioxine-5-yl)-piperazine-1-yl)-ethyl)-methyl-amino)-2H-pyridazine-3-one

C = 4-chloro-5-(2-(4-(2,3-dihydro-1,4-benzodioxine-5-yl)-piperazine-1-yl)-ethylamino)-2-methyl-2H-pyridazine-3-one

D = 5-(3-(4-(2,3-dihydro-1,4-benzodioxine-5-yl)-piperazine-1-yl)-propylamino)-2H-pyridazine-3-one

E = 5-{2-[4-(4-fluoro-phenyl)-piperazine-1-yl]-ethylamino}-2H-pyridazine-3-one

F = 5-{2-[4-(7-chloro-2,3-dihydro-benzo[1,4]dioxine-5-yl)-piperazine-1-yl]-ethylamino}-2H-pyridazine-3-one

G = 5-((2-(4-(2,3-dihydro-benzo[1,4]dioxine-5-yl)-piperazine-1-yl)-ethyl)-methyl-amino)-2-methyl-2H-pyridazine-3-one hydrochloride